UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,567	04/07/2005	Alan Barge	056291-5203	8992

9629 7590 12/04/2007

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
FINN, MEGHAN R	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
12/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,567	BARGE, ALAN	
	Examiner	Art Unit	
	Meghan Finn	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/07/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The information disclosure statement filed April 7, 2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

The listing of references in the Search Report is not considered to be an information disclosure statement (IDS) complying with 37 CFR 1.98. 37 CFR 1.98(a)(2) requires a legible copy of: (1) each foreign patent; (2) each publication or that portion which caused it to be listed; (3) for each cited pending U.S. application, the application specification including claims, and any drawing of the application, or that portion of the application which caused it to be listed including any claims directed to that portion, unless the cited pending U.S. application is stored in the Image File Wrapper (IFW) system; and (4) all other information, or that portion which caused it to be listed. In addition, each IDS must include a list of all patents, publications, applications, or other information submitted for consideration by the Office (see 37 CFR 1.98(a)(1) and (b)), and MPEP § 609.04(a), subsection I. states, "the list ... must be submitted on a separate paper." Therefore, the references cited in the Search Report have not been considered. Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date of submission for purposes of determining

compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP § 609.05(a).

Specification Objections

The disclosure is objected to because of the following informalities: The title is not descriptive. A suggested title is "Combination therapy comprising ZD6474 and gemcitabine for anti-cancer therapy". Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 6-8, and 12-14 provide for the use of a composition comprising ZD6474 and gemcitabine, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 6-8, and 12-14 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an

improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant claims a "method for the production of an antiangiogenic and/or vascular permeability reducing effect" in claims 1 and 9. This method is not enabled by the specification. Applicant has not shown how the method of the instant case would affect antiangiogenic or vascular permeability effects in any way, and thus one of skill in

the art would not be able to use the composition of the instant case to use the invention as claimed.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount of direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The quantity of experimentation required is large (1) due to the unclear language of the claims, and the total lack of direction (2) or examples towards vascular permeability or antiangiogenic effects (3). The nature of the invention is treatment of humans (4) and the state of the prior art is such that reducing vascular permeabitlity or producing anti-angiogenic effects cannot be practiced without at least some direction (5). The relative skill of those in the art is high (6), however most cancer related treatments are complicated and unpredictable (7) and the breath of the claims is large (8) due to the lack of clarity on what exactly the applicant intends to claim.

Claims 2-3, and 10-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the reduction of tumor growth in

pancreatic cancer, does not reasonably provide enablement for treatment of cancer as a whole. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims encompass treating all forms of cancer, since no type or symptoms of cancer have been claimed. As is commonly known in the art, cancer is an incredibly complex and varying disease, and it takes a large amount of information to enable one of skill in the art to use a single composition to treat all forms of cancer.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount of direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The quantity of experimentation required is large (1) due to the lack of direction for treating generic cancer (2) there are examples towards reducing tumor growth in pancreatic cancer (3), which is direction towards treatment of pancreatic cancer, but the

specification lacks examples or rationale for how this invention can treat other forms of cancer. The nature of the invention is treatment of humans (4) and the state of the prior art is such that treatment of cancer is complicated (5) and unpredictable (7). The relative skill of those in the art is high (6), however the breath of the claims is large (8) due to the fact that cancer is generically claimed and is a varied and complex disease for which one treatment option is not usually useful for more than a few forms of cancer.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant claims "A method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human". It is unclear whether applicant is claiming a method of production or reduction of antiangiogenic/vascular permeability. It could be interpreted that the claim is a method of producing antiangiogenic effects or reducing vascular permeability. Alternatively it could be interpreted that applicant is claiming a increase in the antiangiogenic/vascular permeability reducing effects. In any case, it is not clear what applicant intends to

claim, and as such claims 1 and 9 fail to distinctly point out the subject matter to which the applicant regards as the invention.

Claims 6-8 and 12-14 are also rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. Claims 6-8, and 12-14 provide for the use of a composition comprising ZD6474 and gemcitabine, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. Thus the claims fail to distinctly point out the subject matter to which applicant regards as the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-8, 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruns et al (Effect of the Vascular Endothelial Growth Factor Receptor-2 Antibody DC101 Plus Gemcitabine on Growth Metastasis and Angiogenesis of Human Pancreatic Cancer Growing Orthotopically in Nude Mice, cited by applicant on page 3 of specification) in view of Sepp-Lorenzino et al. (Antiangiogenic agents targeting vascular endothelial growth factor and its receptors in clinical development).

Claim 1 claims a method of reducing vascular permeability comprising administering ZD6474 and gemcitabine. Bruns et al. teaches using gemcitabine with a VEGF-R2 antibody agent DC101 to treat pancreatic cancer (page 101, column 2, paragraph 2). Bruns et al. teach that inhibition of VEGF R-2 is an effective way to inhibit angiogensis (page 101, column 2, paragraph 1) and that both KDR and VEGF-R2 receptors are involved in vessel growth and pancreatic cancer (page 101, column 1, paragraph 1), however, they do not teach the combination of ZD6474 with gemcitabine.

Sepp-Lorenzino et al. teach many different VEGF inhibitors and their use in inhibiting angiogensis (abstract). Specifically they teach that ZD6474 is a Potent KDR receptor inhibitor (page 1453, section 2.3, line 1) and that ZD6474 inhibits vascular permeability (page 1454, column 1, paragraph 2). Sepp-Lorenzino et al. also teach several VEGF inhibitors are used in combination with gemcitabine, SU5416 (page 1450, column 2, paragraph 4) and CEP-7055 (page 1455, column 2, paragraph 1). They further teach that the same antiangiogenic agents which act on KDR receptors also act on VEGF R-2 receptors (page 1448, figure 1). Thus, it would have been obvious to one or ordinary skill in the art at the time of the invention to substitute ZD6474 (a VEGF inhibitor which acts at KDR) for DC101 (a VEGF-R2 inhibitor) in the method of Bruns et al. since ZD6474 is known to treat vascular permeability and both compounds Inhibit the same VEGF receptor. It is common practice in optimization of cancer therapies to substitute a drug that has good efficacy for the same receptor if it would also have other benefits (known ability to reduce vascular permeability). Thus claim 1 is unpatentable over Bruns et al. in view of Sepp-Lorenzino et al.

In claim 2, applicant claims a method of treating cancer. Both Bruns et al. and Sepp-Lorenzino et al. teach drugs that are useful for treatment of various cancers, and angiogenesis is known to play a role in cancer, thus for the reasons disucssed above it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute ZD6474 for DC101 in the method of Bruns et al. due to the potency of

ZD6474 and its known antiangiogenic properties. Thus claim 2 is also unpatentable over over Bruns et al. in view of Sepp-Lorenzino et al.

Claims 4 and 5 claim a pharmaceutical composition and a kit comprising ZD6474 and gemcitabine. Since the method of treatment of cancer with that combination is obvious as discussed supra, the composition and the use of the composition in a "kit" form is obvious as well. Thus claims 4 and 5 are unpatentable over over Bruns et al. in view of Sepp-Lorenzino et al.

Claims 6-8, and 12-14 are use claims, and are reject under USC 101 for failing to distinctly point out the steps involved in their use. Use claims could be interpreted as either composition or method claims, however in either case the use claims would read on either the method claims of 1-3 or 9-11 or the composition claims of 4-5 and thus would be obvious over Bruns et al. in view of Sepp-Lorenzino et al.

Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruns et al (Effect of the Vascular Endothelial Growth Factor Receptor-2 Antibody DC101 Plus Gemcitabine on Growth Metastasis and Angiogenesis of Human Pancreatic Cancer Growing Orthotopically in Nude Mice, cited by applicant on page 3 of specification) in view of Sepp-Lorenzino et al. (Antiangiogenic agents targeting vascular endothelial growth factor and its receptors in clinical development) in further view of

Ostruszka et al. (The Role of Cell Cycle Progresion in Radiosensitization by 2',2'-difluoro-2'-deoxycytidine).

Claims 9 and 10 are the same as claims 1 and 2 respectively, except that claims 9 and 10 further add the composition is administered before, after or simultaneously with an effective amount of ionizing radiation. If the composition is administered before the ionizing radiation then they are the same method as claims 1 and 2. Neither Bruns et al. or Sepp-Lorenzino et al. teach the combination therapy including use of ionizing radiation, however the use of ionizing radiation in cancer therapy is well known and it is often used in combination with anti-cancer drugs such as those in the instant invention.

Ostruszka et al. teaches that gemcitabine (also referred to as dFdCyd) can be used in combination with ionizing radiation (abstract) and that gemcitabine is a potent radiosensitizer (abstract). Thus one of ordinary skill in the art at the time of the invention would be aware of ionizing radiation and the fact that it works in combination with anti-cancer drugs such as gemcitabine, and thus it would have been obvious to one of ordinary skill at the time of the invention two also add ionizing radiation to the combination therapy in claims 1 and 2 and thus claims 9 and 10 are unpatentable over Bruns et al. in view of Sepp-Lorenzino et al., in further view of Ostruszka et al.

Claims 3 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruns et al (Effect of the Vascular Endothelial Growth Factor Receptor-2 Antibody DC101 Plus Gemcitabine on Growth Metastasis and Angiogenesis of Human

Pancreatic Cancer Growing Orthotopically in Nude Mice, cited by applicant on page 3 of specification) in view of Sepp-Lorenzino et al. (Antiangiogenic agents targeting vascular endothelial growth factor and its receptors in clinical development), in further view of Ostruszka et al. (The Role of Cell Cycle Progresion in Radiosensitization by 2',2'-difluoro-2'-deoxycytidine), in further view of Burton et al. (US 2003/0096875 A1).

Claims 3 and 11 involve the method of treating as claimed in claims 2 and 10, which are discussed supra, and further specify that the method of treating cancer involving a solid tumor. Neither Bruns et al. or Sepp-Lorenzino et al. explicitly state whether their methods can be used on solid tumors. Ostruszka et al. teach that gemcitabine has clinical activit y in treatment of solid tumors (page 6080, paragraph 1) and Burton et al. teach that ZD6474 can be used on solid tumors (page 12, table 13). Thus it would have been obvious to one of ordinary skill in the art at the time of the invention that if the combination of ZD6474 and gemcitabine can be used to treat cancer as discussed supra, and both drugs are individually known to treat solid tumors, that the combination would be expected to also treat solid tumors.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Salvati and Lee et al. are relevant to applicant's invention and as such are cited to show the state of the art at the time of the invention.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Meghan Finn whose telephone number is (571) 270-3281. The examiner can normally be reached on 7:30am-5pm Mon-Thu, 7:30am-4pm Friday (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Meghan Finn

12/1/07

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER